REMARKS/ARGUMENTS

Claims 1 and 3-29 were pending in the above-identified application. Claims 4-7, 10-12, 16, and 24-29 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1, 3, 8-9, 13-15, and 17-23 have been acted upon by the Examiner. Claim 1 has been amended to set forth the present invention with greater particularity. No new matter is added by this amendment. In light of the amendment and the remarks and arguments set forth below, Applicants respectfully request reconsideration of the application.

Rejections under 35 U.S.C. § 112

Claims 1, 3, 8-9, 13-15, 17-23 remain rejected under 35 U.S.C. § 112, first paragraph, because the Examiner alleges that while the specification is enabling for a method for differentiating human monocytic dendritic cell precursors into immature dendritic cells having CD1a on the cell surface, the specification does not reasonably provide enablement for a method for differentiating monocytic dendritic cell precursors into immature dendritic cells having CD1a on the cell surface.

Although Applicants do not agree with the rejection or reasoning of the Examiner claim 1 has been amended to recite the invention with greater particularity. In particular, claim 1 has been amended to recite a method for differentiating human monocytic dendritic cell precursors into immature dendritic cells including a step comprising providing a cell population comprising non-activated human monocytic dendritic cell precursors. Such amendment is believed to obviate the rejection of the Examiner and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under U.S.C. § 102

Claims 1, 3, 8, 9, 14, 17 - 19, and 23 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bernard *et al.*, 1998 (of record). Bernard *et al.* is alleged by the Examiner to teach a method comprising culturing non-activated monocytes (*i.e.*, a monocytic dendritic cell

precursor) with GM-CSF alone in a TEFLON™ culture bag (*i.e.*, a bag comprising PFTE, see page 18 - 19 in particular). Bernard *et al.* is alleged to further teach that the culture system is adherent free, and that the resulting cells express CD1a (see Fig. 2, in particular). Bernard *et al.* is also alleged to teach that the monocytes are isolated by apheresis and contacting the $CD1a^+$ cells with the bacterial antigen tetanus toxoid.

The Examiner also believes that the instant claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (*i.e.*, a method of using a product made by a particular process). The Examiner notes that the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structurally difference. The monocytic dendritic cell precursors of Bernard *et al.* are asserted by the Examiner to be the same as those produced by tangential flow filtration. Additionally, the Examiner has asserted that while Bernard *et al.* do not characterize the $CD1a^+$ cells as immature dendritic cells, they must inherently be immature dendritic cells, since they are produced by a method identical to that of the instant claims. Based on these allegations, the Examiner asserts that the reference clearly anticipates the invention.

Applicants respectfully disagree with the rejection of claims 1, 3, 8, 9, 14, 17 - 19, and 23 as being anticipated by Bernard *et al.* In particular, Bernard *et al.* do not disclose a method of differentiating dendritic cells by culturing in GM-CSF alone without any additional cytokines. At page 21, right column, lines 1-3 Bernard *et al.* described results of culturing elutriated monocytes in GM-CSF and IL-4 in hydrophobic bags to differentiate into immature dendritic cells. A method for the production of macrophage is also disclosed. In this method monocytes were cultured with GM-CSF alone. The macrophage were characterized by the absence of significant neo-expression of CD1a and CD1c, a much lower expression of HLA DQ molecules and an up-regulation of CD14. See page 21, right column 26 - 32. As such, Bernard *et al.* do not anticipate the method of the present invention.

The Examiner has also asserted that the monocytic dendritic cell precursors of Bernard *et al.* are inherently identical to the monocytic dendritic cell precursors produced by

tangential flow filtration. As there is no characterization of the precursor cells following elutriation, the Examiner has no basis to make this assertion. The fact that IL-4 was apparently necessary to prevent differentiation of the precursor cells of Bernard *et al.* when cultured in "non-adherent" conditions would suggest that the precursor cells may have been activated during elutriation or that there is a factor in the culture media of Bernard *et al.* that is activating the cells to differentiate without IL-4. As such, Applicants do not believe that the Examiner has demonstrated that the dendritic precursor cells of Bernard are inherently identical to the precursor cells of the present invention.

Applicants respectfully request that the rejection of claims 1, 3, 8, 9, 14, 17 - 19, and 23 as being anticipated by Bernard *et al.* be reconsidered and withdrawn in view of the above remarks.

Rejections under U.S.C. § 103

Claims 1, 3, 8, 9, 13, 14, 17 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Matera *et al.*, 2000, in view of Bernard *et al.*, 1998 (above). In particular, the Examiner alleges that Matera *et al.* teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (*i.e.*, non-activated), and contacting the monocytes with GM-CSF in the absence of additional cytokines citing to page 30 and 31 in particular. Matera *et al.* is also alleged by the Examiner to teach culturing in a serum free medium and to teach that the dendritic cells generated by culture with GM-CSF alone express CD1a. The Examiner has also alleged that the monocytic dendritic cell precursors of Matera *et al.* are the same as those produced by tangential flow filtration. Matera *et al.* acknowledged by the Examiner not to teach a low avidity culture vessel comprising PFTE.

As above, Bernard *et al.* is alleged by the Examiner to teach a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON™ (comprising PFTE) bag. Furthermore, the Examiner has alleged that Bernard *et al.* teaches that the method meets

good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells. Therefore, the Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cells taught by Matera *et al.*, using the TEFLON™ culture vessel, as taught by Bernard *et al.*. Motivation for the ordinary artisan at the time the invention was made would have been provided since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of dendritic cells in a culture system that meets GLP procedures. Moreover, one of ordinary skill in the art would have a reasonable expectation of success.

Applicants respectfully disagree with the rejection of claims 1, 3, 8, 9, 13, 14, 17 and 18 as being unpatentable under 35 U.S.C. § 103(a) over Matera *et al.*, 2000, in view of Bernard *et al.* Matera *et al.* is alleged by the Examiner to teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting and contacting the monocytes with GM-CSF in the absence of additional cytokines. To the contrary, Matera *et al.* disclose a method for producing macrophage comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting and contacting with GM-CSF alone. Applicants respectfully direct the Examiner to page 32, right column, lines 3-5 where the authors report that GM-CSF was very effective at inducing macrophage-like cells and cells of typical DC morphology developed in sets stimulated with GM-CSF plus IL-4. Bernard *et al.* is described above, and like Matera *et al.* described methods where macrophage are developed when monocytic dendritic cell precursors are cultured in the presence of GM-CSF alone. There is no disclosure in either reference that suggests or teaches the present invention. The Examiner is respectfully requested to therefore withdraw the present rejection.

Claims 19-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Matera *et al.* and Bernard *et al.*, as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, in further in view of Bosch *et al.*, 2001 (of record). The teachings of Matera *et al.* and Bernard *et al.* are described above. The Examiner has acknowledged that they not teach generating maturing the dendritic cells with IFNγ and BCG. Bosch *et al.* is alleged by the Examiner to teach that

dendritic cells can be matured with a combination of INFγ and BCG (*i.e.*, a bacterial antigen). Additionally, Bosch *et al.* is alleged by the Examiner to teach that maturation with IFNγ and BCG results in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients.

Therefore, the Examiner has asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a dendritic cell, as taught by Matera *et al.* and Bernard *et al.*, followed by maturation with BCG and IFNγ as taught by Bosch *et al.*. The Examiner has asserted that the ordinary artisan would have been motivated to do so, since Bosch *et al.* teach that IFNγ and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients. Moreover, the Examiner believes that one of ordinary skill in the art would have a reasonable expectation of success, since Bosch *et al.* teaches the effectiveness of these techniques in the generation of dendritic cells.

Applicants respectfully disagree with the rejection of claims 19-23 as being unpatentable over Matera *et al.* and Bernard *et al.*, as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, in further in view of Bosch *et al.*, 2001. Matera *et al.* and Bernard *et al.* are discussed above. Both references describe methods that require both GM-CSF and IL-4 for the differentiation of immature dendritic cells from isolated monocytic dendritic cell precursors. Bosch *et al.* disclose a similar method for the production of immature dendritic cells. Bosch *et al.* also disclose the maturation of dendritic cells in the presence of BCG and IFNγ for the induction of an antigen specific cytotoxic T cell response. But, the references when considered alone or in any combination fail to teach a method for the production of immature dendritic cells from non-activated monocytic dendritic cell precursors in the presence of GM-CSF alone as presently claimed. As such, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 19-23 as being unpatentable over Matera *et al.* and Bernard *et al.* in further view of Bosch *et al.*

Claim 15 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Matera *et al.* and Bernard *et al.* as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, and further in view of Lewalle *et al.*, 2000 (of record). The alleged teachings of Matera *et al.* and Bernard *et al.* are described above. The Examiner has acknowledged they do not teach using a cryopreserved cell population to generate dendritic cells. Lewalle *et al.* is alleged by the Examiner to teach the generation of dendritic cells from frozen peripheral blood mononuclear cells. Furthermore, Lewalle *et al.* is alleged by the Examiner to teach that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Based on these allegations and assertions that Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cell taught by Matera *et al.* and Bernard *et al.*, using frozen peripheral blood mononuclear cells, as taught by Lewalle *et al.*. Motivation for the ordinary artisan at the time the invention was made is alleged by the Examiner to be based on Lewalle *et al.* teaching that many clinical protocols are based on sequential injections of dendritic cells, and the practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Furthermore, the Examiner believes that the ordinary artisan would have had a reasonable expectation of success since Lewalle teaches that dendritic cells derived from frozen peripheral blood mononuclear cells retain their functional capacity.

Applicants respectfully disagree with the rejection of claim 15 as being unpatentable over Matera *et al.* and Bernard *et al.* as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, and further in view of Lewalle *et al.*, 2000. As above, Matera *et al.* and Bernard *et al.* when considered either alone or in any combination fail to teach the methods of the present invention. Lewalle *et al.* also does not disclose or suggest a method for differentiating human monocytic dendritic cell precursors into immature dendritic cells having CD1a on the cell surface, comprising: providing a cell population comprising non-activated human monocytic dendritic cell precursors, and contacting the non-activated monocytic dendritic cell precursors in a culture vessel with a dendritic cell culture media supplemented with granulocyte-macrophage

colony stimulating factor in the absence of additional cytokines under conditions that do not activate the monocytic dendritic cell precursors. As such, Lewalle *et al.* does not provide any feature of the invention that is not disclosed in Matera *et al.* and/or Bernard *et al.* Lewalle *et al.* is directed to the generation of dendritic cells from frozen peripheral blood mononuclear cells. Such a disclosure does not teach or suggest any method for the production of immature dendritic cells having CD1a on their surface. The references when considered either alone or in any combination also do not provide or suggest that the skilled artisan would have any reasonable expectation of success in developing such a method. Therefore, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 15 as being unpatentable over Matera *et al.* and Bernard *et al.*, and further in view of Lewalle *et al.*

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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